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EXAMINER	
CHEN, SHIN LIN	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 05/26/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/913,427	YOUNG ET AL.	
	Examiner	Art Unit	
	Shin-Lin Chen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 August 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) *2,16 and 17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-15 and 18-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10-12-01, 11-8-01*. 11-16-01
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election with traverse of group I, claims 1 and 3-25, in the response to restriction requirement filed 8-25-03 is acknowledged. The traversal is on the ground(s) that the special technical feature for groups I and II is the use of neural progenitor cells derived from an adult donor, which was not taught by the references cited by examiner. This is not found persuasive because Reid teaches contacting CNS neural progenitor cells with a polypeptide that binds the EGF receptor and directing progeny of the proliferating progenitor cells to CNS region where they reside and function in a manner to reduce the neurological deficit. Reid does teach using neural progenitor cells derived from an adult donor. Further, Gage et al., 1995 (PNAS, Vol. 92, p. 11879-11883) teach culturing neural progenitor cells isolated from adult rat hippocampus and transplanting said cells back into adult rat hippocampus. Thus, the use of neural progenitor cells derived from adult donor is not contributed by the present invention over the prior art.

The requirement is still deemed proper and is therefore made FINAL.

It should be noted that claims 16 and 17 solely depend on claim 2 and were put in group I by mistake. Since claim 2 is directed to non-elected invention, therefore, claims 16 and 17 are also drawn to non-elected invention.

2. Claims 2, 16 and 17 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the response to restriction requirement filed 8-25-03.

Claims 1-25 are pending and claims 1, 3-15 and 18-25 are under consideration.

Specification

3. Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to **a single paragraph on a separate sheet** within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

The abstract filed 8-10-01 is a front page of a WO publication but not a single paragraph on a separate sheet. Appropriate correction is required.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1, 3-15 and 18-25 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: whether the symptom of dystrophic neural tissue has been ameliorated. The method only states introducing neural progenitor cells into dystrophic neural tissue but it is unclear what happens after said neural progenitor cells are introduced into said dystrophic neural tissue. Claims 3-15 and 17-25 depend on claim 1 but fail to clarify the indefiniteness.

6. Claims 1, 3-15 and 18-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "derived from" in claim 1 is vague and renders the claim indefinite. It is unclear as to the metes and bounds of what would be considered "derived from". It is unclear whether the phrase "derived from" refers to the cells that are naturally occurring cells or cells that have been modified with genetic materials or chemicals, or other means of modification. The specification fails to specifically define the phrase "derived from". Claims 3-15 and 18-25 depend on claim 1 but fail to clarify the indefiniteness.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1, 3-15 and 18-25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for preparation of adult rat hippocampal progenitor cells (AHPCs) isolated and cultured from adult rat hippocampus, expression of GFP in various cells in host retina as disclosed when AHPCs were injected into the vitreous or subretinal space of an eye, differentiation of the injected AHPCs into neurons with morphological characteristics suggestive of native retina cell types in mice or rats, and some behavioral recovery as measured by optokinetic nystagmas (OKN) reflex testing rats, does not reasonably provide enablement for a method of treating various dystrophic neural tissues in an animal recipient by introducing neural progenitor cells derived from various parts of central nervous system (CNS) of an adult animal donor via various administration routes. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are directed to a method of treating dystrophic neural tissues in an animal recipient by introducing neural progenitor cells derived from an adult animal donor, such as brain tissue, hippocampus, ventricular zone, into dystrophic neural tissue, such as CNS, an eye, an optic nerve, and a vitreous, in an animal recipient, for example, an immature animal, an adult, and a human. Claims 11-15 specify the donor and recipient are of different species or same species, or syngeneic. Claims 18-24 specify the neural progenitor cells are cultured in vitro in culture medium comprising at least one trophic factor, such as a neural growth factor, a neurotrophin, a cytokine, a growth factor etc.

The specification discloses preparation of adult rat hippocampal progenitor cells (AHPCs) isolated and cultured from adult rat hippocampus, expression of GFP in various cells in host retina as disclosed when AHPCs were injected into the vitreous or subretinal space of an eye, differentiation of the injected AHPCs into neurons with morphological characteristics suggestive of native retina cell types in mice or rats, and some behavioral recovery as measured by optokinetic nystagmas (OKN) reflex testing rats. The claims encompass treating various dystrophic neural tissues in an animal recipient by introducing neural progenitor cells derived from various parts of central nervous system (CNS) of an adult animal donor via various administration routes. The dystrophic neural tissues encompass damaged, injured, or diseased neural tissues derived from numerous neural diseases or disorders, including Huntigton's disease, Wilson's disease, Parkinson's disease, ALS and variants thereof, spinal cerebellar ataxia, parepheral neuropathy, retinal neuronal degeneration, Alzheimer's diseaseepilepsy, and lysosomal storage disorders etc. (see specification, pages 5-6).

The specification fails to provide adequate guidance and evidence for how to isolate and culture neural progenitor cells from various parts of CNS of an adult animal. The specification fails to provide adequate guidance and evidence for how to use the claimed neural progenitor cells to treat numerous dystrophic neural tissues derived from various neural diseases or disorders so as to provide therapeutic effect in the animal recipient either allogeneic, syngeneic, or of different species via various administration routes.

The state of the art of neural progenitor cells derived from adult donor indicates that there are limited areas that can produce neural progenitor cells. Shihabuddin et al., November 1999 (Molecular Medicine Today, Vol. 5, No. 11, p. 474-480) report that "[T]here are two areas of the adult brain that continue to generate neurons throught adult life: the subgranular zone in the dentate gyrus of the hippocampus and the forebrain subventricular zone (SVZ) (e.g. page 475, right column). There is no evidence of record that areas in the adult brain of any animal other than the disclosed dentate byrus of hippocampus and SVZ can produce neural progenitor cells for treating numerous different dystrophic neural tissues as claimed. Although Shihabuddin suggests that the progenitor cells from CNS have a wide developmental potential and can respond to persistent neuronal differentiation signals in the adult CNS and neural stem cells may have much broader differential potential than previously thought, however, Shihabbdin points out that "[A] key issue is whether stem cells can survive and differentiate following grafting into the adult CNS" and "[G]iven the complexity of the nervous system, the pathological milieu in different neurodegenerative diseases and the variability within each disease, it is possible that repair strategies might involve a combination of transplantation, recruitment of endogenous repair mechanisms and genetic manipulation of donor tissue in order to generate cells ideally

suited to the delivery of therapeutic substances that prevent cell loss and promoter regeneration and functional recovery" (e.g. 478, 480, left column).

Luskin, M., 1998 (US Patent 5,753,505) reports that "Several difficulties have arisen, however, in identifying sources ofr dividing cells that generate neurons because neuronal progenitor cells frequently fail to express neuronal markers and because heterogeneous populations of cells (including neuronal and non-neuronal cells) generally arise (e.g. column 1, lines 21-25). "Sources of neuronal precursors from adult and neonatal mammalian nervous systems have generally resulted in similar problems with heterogeneity" (e.g. column 1, lines 50-52). "[N]euronal cells which differentiate and eventually cease dividing result in a decreased likelihood of tumor formation when transplanted into a host nervous system. Glia, in contrast to neurons, can be highly proliferative when given certain signals and can even form gliomas. Neoplastic cell lines can similarly result in tumor formation" (e.g. column 2, lines 29-36).

In view of the evidence set forth above, there are limited sources of neural progenitor cells derived from an adult animal donor, i.e. cells isolated and cultured from the subgranular zone in the dentate gyrus of the hippocampus and the forebrain subventricular zone (SVZ). There are also difficulties in isolating homogenous neural progenitor cells from an adult donor. Heterogeneous cells including non-neuronal cells are the common problems in isolating neural progenitor cells from adult or neonatal mammalian nervous system. The specification fails to provide adequate guidance and evidence for how to isolate and culture neural progenitor cells from various parts of CNS of an adult animal donor other than hippocampus and SVZ. The specification also fails to provide adequate guidance and evidence for how to use the neural progenitor cells, which could have heterogeneous cell populations, to treat numerous dystrophic

neural tissues derived from various neural diseases or disorders so as to provide therapeutic effect in the animal recipient either allogeneic, syngeneic, or of different species via various administration routes, such as intravenous injection, intraperitoneal injection, intramuscular injection, oral administration etc. Different administration routes of the neural progenitor cells to dystrophic neural tissue in an animal recipient would result in different effect in said animal recipient. There is no evidence of record that introduction of a neural progenitor cells into dystrophic neural tissue via various administration routes, such as intravenous injection, intraperitoneal injection, intramuscular injection, oral administration etc., could provide therapeutic effect for said dystrophic neural tissue in vivo. Thus, one skilled in the art at the time of the invention would not know how to use the claimed neural progenitor cells to treat dystrophic neural tissues derived from numerous neuronal diseases and disorders such that therapeutic effect could be obtained in vivo via various administration routes.

For the reasons discussed above, it would have required undue experimentation for one skilled in the art at the time of the invention to have made and used the invention over the full scope claimed. This is particularly true given the nature of the invention, the state of the prior art, the breadth of the claims, the amount of experimentation necessary, the working examples provided, and scarcity of guidance in the specification, and the unpredictable nature of the art.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 1, 3-15 and 18-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gage et al., 1995 (PNAS, USA, Vol. 92, p. 11879-11883, IDS) in view of Weiss et al., 1997 (WO 97/35605, IDS).

The claims are directed to a method of treating dystrophic neural tissues in an animal recipient by introducing neural progenitor cells derived from an adult animal donor, such as brain tissue, hippocampus, ventricular zone, into dystrophic neural tissue, such as CNS, an eye, an optic nerve, and a vitreous, in an animal recipient, for example, an immature animal, an adult, and a human. Claims 11-15 specify the donor and recipient are of different species or same species, or syngeneic. Claims 18-24 specify the neural progenitor cells are cultured in vitro in culture medium comprising at least one trophic factor, such as a neural growth factor, a neurotrophin, a cytokine, a growth factor etc.

Gage teaches preparation of neural progenitor cells capable of proliferation and neurogenesis by isolating and culturing cells from the adult rat hippocampus and the cells can survive, proliferate and express neuronal and glial markers in a defined medium containing FGF-

2. The FGF-2 responsive progenitor cells retain the capacity to generate mature neurons when grafted into the adult rat brain (e.g. abstract).

Gage does not teach using the prepared neural progenitor cells to treat dystrophic neural tissues, wherein the donor and recipient animals are of same species or different species.

Weiss teaches in vivo proliferation of multipotent neural stem cells in the hippocampus of a mammal by administering at least one growth factor, for example, epidermal growth factor and/or fibroblast growth factor, to the hippocampal region to induce proliferation of stem cells to produce stem cells progeny that are capable of differentiating into neurons and glial cells. Weiss also teaches a method of treating neurological diseases, injuries, or disorders which affect the hippocampal region of the brain, such as stroke (e.g. abstract, p. 12).

It would have been obvious for one of ordinary skill in the art at the time of the invention to use the FGF-2 responsive progenitor cells from the adult rat hippocampus as taught by Gage to treat neurological diseases, injuries, or disorders which affect the hippocampal region of the brain as taught by Weiss because the in vitro cultured neural progenitor cells retain the capacity to generate mature neurons when grafted into the adult rat brain and Weiss teaches producing such progenitor cells by injecting growth factor in vivo to treat neurological diseases or disorders. It also would have been obvious for one of ordinary skill in the art to use neural progenitor cells from an animal donor to treat an animal recipient of same species or different species because it was well known in the art to use organs or tissues of same or different species for transplantation, it is obvious that the donor and recipient are of same or different species in order to achieve optimized therapeutic effect.

One having ordinary skill in the art at the time the invention was made would have been motivated to do so in order to treat neurological diseases, injuries, or disorders which affect the hippocampal region of the brain, such as stroke, as taught by Weiss with reasonable expectation of success. It should be noted that the claimed method only indicates treating dystrophic neural tissue in the preamble but fails to specify what therapeutic effect is expected. Therefore, it is obvious for one of ordinary skill to practice the claimed methods according to the collective teachings of Gage and Weiss with reasonable expectation of success.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (571) 272-0726. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on (571) 272-0804. The fax phone number for this group is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

Shin-Lin Chen, Ph.D.

SHIN-LIN CHEN
PRIMARY EXAMINER